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EDITORIAL COMMENT

Endothelin and the Systemic Circulation

A Therapeutic Target Worth Revisiting?*

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Endothelin (ET)-1, one of the most potent endogenous vasoconstrictors and promoters of vascular growth, is produced by vascular endothelial cells in response to a variety of stimuli (1,2). The development of ET receptor antagonists (3) facilitated the exploration of the pathophysiological role of ET-1 in a variety of diseases in which ET-1 expression is increased, including systemic hypertension (4), congestive heart failure (5), Raynaud's phenomenon and digital ulcers in scleroderma (6), pulmonary arterial hypertension (7), and idiopathic pulmonary fibrosis (8). Despite large-scale clinical trials in these conditions, ET receptor antagonists have been demonstrated to have convincing clinical effects only in pulmonary arterial hypertension, the sole condition for which both the dual ET-A and ET-B receptor antagonist bosentan and the more selective ET-A receptor antagonist ambrisentan have received approval by the Food and Drug Administration. In this issue of the *Journal*, Belaidi et al. (9) provide evidence that ET-1 may play a more significant role in the systemic circulation under certain conditions, specifically intermittent hypoxia in the background of a predisposition for systemic hypertension, and suggest that the clinical scenario that they sought to mimic in their studies—obstructive sleep apnea (OSA)—may benefit from therapy with ET receptor antagonists.

See page 1309

Belaidi et al. (9) exposed control and spontaneously hypertensive rats to intermittent hypoxia designed to mimic the frequent intervals of apnea that are experienced by individuals with severe, uncontrolled OSA, and found that the spontaneously hypertensive rats, but not control rats, manifested greater increases in blood pressure and coronary vasoreactivity along with increased expression of ET-1 and hypoxia-inducible transcription factor (HIF)-1. In addition, the administration of bosentan blocked these augmented systemic vascular responses. They suggest that HIF-1 mediates the increased ET-1 expression in their model.

OSA is a common disorder that has been increasingly recognized as a significant contributing factor to cardiovascular morbidity and mortality, including both systemic hypertension and heart failure (10,11). Although lifestyle changes, such as weight loss and avoidance of alcohol and other sedatives, are effective in some patients with OSA, these are not always contributory factors, and other active measures for management are often needed. Continuous positive airway pressure applied at night is an effective, albeit cumbersome, therapy for OSA that, when adjusted to the patient's individual requirements and used consistently, effectively reverses nocturnal hypoxemia and may reduce the comorbid cardiovascular events. Technological advances in this field have improved the diagnostic approach to OSA as well as patient comfort and compliance with the hardware used for its treatment. It is unlikely, therefore, that, given the expense and toxicities of ET receptor antagonists, these agents will have much advantage over current therapy for OSA, although studies in OSA patients who have persistent cardiovascular comorbidities despite continuous positive airway pressure therapy may be of potential interest. Perhaps more worthy of study are other conditions in which intermittent hypoxia coexists with systemic vascular disease, notably the aging population with smoking-related chronic obstructive pulmonary disease and coexistent systemic hypertension or arteriosclerotic heart disease: while an extrapolation from the studies of Belaidi et al. (9) to this clinical condition is equally fraught with limitations, the medical need is considerable and the rationale is strengthened by their findings.

The experiments presented by Belaidi et al. (9) provide evidence that HIF-1 and ET-1 interact in experimental conditions that are related, but not identical, to human disease. Whether this observation will translate to a new therapeutic target for ET receptor antagonists is unclear, but it at least provides a rationale for exploring the effects of these drugs in relevant populations for which novel approaches to therapy are needed.

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